GUIDE FOR DOCTORS: LONG-TERM CONDITION

BONE MARROW FAILURES AND OTHER CHRONIC CYTOPENIAS
myelodysplastic syndromes

January 2008
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Updated ALD guides and lists

Guides for doctors produced by HAS are revised every three years.

In the meantime, the list of procedures and services (LAP) is revised, at minimum, on a yearly basis. This list is available on the HAS website.

www.has-sante.fr
### I. Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>AIHA</td>
<td>Autoimmune haemolytic anaemia</td>
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<tr>
<td>ALAT</td>
<td>Alanine aminotransferase</td>
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<tr>
<td>ALD</td>
<td>Long-term condition (<em>affection de longue durée</em>)</td>
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<tr>
<td>AML</td>
<td>Acute myeloid leukaemia</td>
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<tr>
<td>APC</td>
<td>Apheresis platelet concentrate</td>
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<tr>
<td>Ara-C</td>
<td>Arabinosylcytosine</td>
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<tr>
<td>ASAT</td>
<td>Aspartate aminotransferase</td>
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<tr>
<td>ATP</td>
<td>Autoimmune thrombocytopenic purpura</td>
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<tr>
<td>ATU</td>
<td>Temporary licence (<em>autorisation temporaire d’utilisation</em>)</td>
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<tr>
<td>BMB</td>
<td>Bone marrow biopsy</td>
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<tr>
<td>BMF</td>
<td>Bone marrow failure</td>
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<tr>
<td>CML</td>
<td>Chronic myeloid leukaemia</td>
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<tr>
<td>CRP</td>
<td>C-reactive protein</td>
</tr>
<tr>
<td>EPO</td>
<td>Erythropoietin</td>
</tr>
<tr>
<td>ESR</td>
<td>Erythrocyte sedimentation rate</td>
</tr>
<tr>
<td>FAB</td>
<td>French-American-British</td>
</tr>
<tr>
<td>FISH</td>
<td>Fluorescent in-situ hybridisation</td>
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<tr>
<td>G-CSF</td>
<td>Granulocyte-colony stimulating factor</td>
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<tr>
<td>GGT</td>
<td>Gamma-glutamyl transferase</td>
</tr>
<tr>
<td>GVH</td>
<td>Graft versus host</td>
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<tr>
<td>Hb</td>
<td>Haemoglobin</td>
</tr>
<tr>
<td>HIV</td>
<td>Human immunodeficiency virus</td>
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<tr>
<td>HLA</td>
<td>Human leucocyte antigen</td>
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<tr>
<td>HSC</td>
<td>Haematopoietic stem cells</td>
</tr>
<tr>
<td>IgG</td>
<td>Immunoglobulin G</td>
</tr>
<tr>
<td>IgM</td>
<td>Immunoglobulin M</td>
</tr>
<tr>
<td>IPSS</td>
<td>International Prognosis Scoring System</td>
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<tr>
<td>LBP</td>
<td>Labile blood products</td>
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<tr>
<td>LGL</td>
<td>Large granular lymphocytes</td>
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<tr>
<td>MA</td>
<td>Marketing authorisation</td>
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<tr>
<td>MDS</td>
<td>Myelodysplastic syndromes</td>
</tr>
<tr>
<td>NL</td>
<td>Neutrophilic leucocyte</td>
</tr>
<tr>
<td>PNH</td>
<td>Paroxysmal nocturnal haemoglobinuria</td>
</tr>
<tr>
<td>SLE</td>
<td>Systemic lupus erythematosus</td>
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<tr>
<td>TSH</td>
<td>Thyroid stimulating hormone</td>
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</table>
1. Introduction

1.1 Objective
The purpose of this guide is to explain to health professionals the optimal management and integrated care pathway for patients with myelodysplastic syndromes.

1.2 Method
The main source documents used to compile this guide were:
- Documents from the Orphanet and French Haematology Society websites
- Italian Society of Haematology *Guidelines*, 2002

The inclusion of these guidelines in the doctor’s guide was discussed and validated by a multidisciplinary working group (Appendix 1).

1.3 General considerations about myelodysplastic syndromes
Myelodysplastic syndromes (MDS) are clonal disorders of the pluripotent or myeloid stem cells. They are characterised by ineffective haematopoiesis, resulting in blood cytopenias which contrast with a generally rich bone marrow (qualitative bone marrow failure with bone marrow cell abortion). MDS often progress to acute myeloid leukaemia (AML) and are the most common preleukaemic states in adults.

MDS predominantly occur in the elderly, the median age at diagnosis being around 70 years. Their overall incidence is 4–5 per 100 000 people per year. Their cause is usually unknown. In 15–20% of cases, MDS are secondary to the use of chemotherapy and/or radiotherapy to treat an existing disease, generally cancer. More rarely, they may be secondary to exposure to benzene or other...
aromatic hydrocarbons, or sometimes to products used in agriculture (pesticides, herbicides or fertilisers).

Primary and secondary MDS may be distinguished on the basis of the patient's clinical history and the notion of exposure to toxic agents, ionising radiation or chemotherapy.

- Primary MDS occur in the absence of a known history or clear exposure to toxic agents. Cytogenetic abnormalities are present at the time of diagnosis in less than 50% of cases, and cytopenia may for a long time involve only one or two cell lineages.
- Secondary MDS are possible complications of chemotherapy, particularly with alkylating agents, and/or exposure to benzene, other aromatic hydrocarbons, herbicides, pesticides or ionising radiation. In most cases these are forms affecting a number of cell lineages. Cytogenetic abnormalities are present in more than 80% of cases.

The treatment options depend on:
- clinical factors (age, general state of health)
- haematological factors (blood and bone marrow cytology)
- cytogenetic factors.

Allogeneic bone marrow transplant is currently the only curative treatment and is reserved for high-risk MDS patients aged below 65–70 years who have a donor.

In high-risk forms where allogeneic transplant is not possible, intensive chemotherapy alone may be proposed for relatively young patients, although it is effective only where the karyotype is normal. It has recently been demonstrated that hypomethylating agents prolong survival; these are active on all karyotypes and may be administered to older patients.

In low-risk forms, management aims essentially at treating the consequences of the cytopenias, especially anaemia, which is the basic problem and may require repeated transfusions of phenotyped packed red blood cells. Iterative transfusions may often be avoided through the use of erythropoietin (EPO) or its derivatives (or lenalidomide in the particular case of chromosome 5q deletion; this is an off-label use that must be initiated and monitored by a specialist and requires regular full blood counts).
2. Initial assessment

2.1 Primary objectives
- Confirm the diagnosis of MDS
- Investigate the cause of this MDS
- Specify the type of MDS
- Establish a prognosis

2.2 Professionals involved

The initial management of an MDS patient involves:
- in all cases:
  - the general practitioner
  - a haematologist.
- depending on the clinical picture, any other specialist whose opinion is necessary, including the doctor responsible for providing the labile blood products (LBP).

2.3 Confirm the diagnosis and investigate the cause

► Interview and clinical examination

The interview and clinical examination above all assess the impact of the cytopenias:
- the clinical impact of the anaemia, in view of the patient’s age and the common comorbidities at that age
- previous infections and their seriousness
- history and signs of haemorrhage
- how long the cytopenias have existed, to give an idea of the progression of the MDS
- aetiological agents: radiotherapy, chemotherapy, immunosuppressors, occupational exposure, particularly to benzene or its derivatives, or ionising radiation; the latter may be grounds for the condition to be declared an occupational disease, with a right to compensation
- associated signs of dysimmune disease, which are particularly frequent in MDS: arthropathy, vasculitis, polychondritis, or even inflammatory bowel disease, etc.
- concomitant medication.

► Additional tests
- Essential tests:
  - biological tests:
Guide – ALD 2 ‘Bone marrow failures and other chronic cytopenias’
Myelodysplastic syndromes

- full blood count with reticulocyte count
- blood smear cytology
- bone marrow examination with blast percentage, evaluation of dysmyelopoiesis and Perls staining to determine the percentage of ring sideroblasts; the examination will show:
  - bone marrow with normal or elevated cell count, or sometimes reduced cell count (hypocellular MDS)
  - morphological abnormalities of one or more cell lineages
  - a variable blast percentage (but less than 20%)
- bone marrow karyotype: this should always be performed except in very old patients in whom the diagnosis of MDS is certain and for whom the karyotype would not affect treatment
- fluorescence in-situ hybridisation (FISH), a test performed by a cytogeneticist using a specific chromosome probe (principally for chromosomes 5, 7 and 8); its use is justified:
  - after two consecutive karyotyping failures, if it may have diagnostic or therapeutic implications for the patient
  - in a case of pancytopenia with a normal karyotype in a young patient, to rule out monosomy 7, which is an independent factor for a poor prognosis
- serum ferritin: before transfusion support is implemented

biochemical tests:
- tests required for differential diagnosis in the forms without excess blasts or to rule out a supplementary cause of anaemia: serum iron and transferrin assay, serum and erythrocyte folate and serum vitamin B12 assay, creatinine assay, liver profile, investigation of an inflammatory syndrome, bilirubin and haptoglobin assay, TSH assay, and HIV and hepatitis B and C serology
- HLA and erythrocyte typing: HLA typing of the patient and his or her siblings should be done systematically if an allogeneic transplant (standard or with reduced-intensity conditioning) or intensive chemotherapy are treatment options considered at some time or other in the progression of the MDS
- erythrocyte phenotyping, essential for all patients.

Recommended tests:
- serum EPO assay in low-risk or intermediate-1-risk MDS, since this is an important prognostic factor for the response to recombinant EPO treatment
screening for a paroxysmal nocturnal haemoglobinuria (PNH) clone.
- Non-recommended tests:
  - bone marrow biopsy (BMB): this is not necessary for diagnosing MDS except in cases where hypocellularity makes the differential diagnosis with bone marrow failure or myelofibrosis difficult, even though dysmyelopoiesis, particularly dysmegakaryopoiesis, is often better described by means of a BMB
  - flow cytometry, currently not standard in MDS (except for CD34 for assessing blastosis).

### 2.4 Specify the type of MDS

The multiplicity of syndromes led in 1982 to the creation of a classification known as the FAB (French-American-British) classification, which puts them into 5 groups (Appendix 2).

A new classification was proposed by WHO in 1999 (Appendix 2).

### 2.5 Establish a prognosis

In 30–40% of cases, the disease progresses to acute myeloid leukaemia (AML) or, if not, to a worsening of the cytopenias.

The International Prognosis Scoring System (IPSS), put forward in 1997, is based on the full blood count, blast percentage and cytogenetic abnormalities.

This score evaluates the risk (low, intermediate or high) of progression to acute leukaemia or death and gives an approximate median survival time.

MDS are classified on the basis of their severity as low-risk MDS (low and intermediate-1 risk groups) and high-risk MDS (intermediate-2 and high risk groups).

### 3. Therapeutic management of myelodysplastic syndromes

#### 3.1 Objectives

The primary objectives of current medical treatment are therefore to:
- slow progression to acute leukaemia and improve patient survival
reduce for as long as possible the impact of the cytopenias on the personal, social and working life of the patient and of the carer givers and family

limit the undesirable effects of treatment as far as possible

improve the patient’s quality of life.

3.2 Professionals involved

The professionals involved in the therapeutic management of MDS patients are:

- in all cases:
  - the general practitioner (for treatment and follow-up)
  - a haematologist (for treatment and follow-up)
- where necessary, specialists other than the haematologist, including the doctor responsible for providing the LBP
- where necessary, ancillary health professionals:
  - nurse
  - psychologist
- where necessary, other professionals:
  - carer givers
  - domestic help
  - social worker.

3.3 Therapeutic patient education and lifestyle adjustments

Therapeutic patient education (TPE) involves all the activities designed to help the patient (and family and friends) understand the disease and its treatments, play a part in the care provided and manage their state of health, and as far as possible to facilitate a return to normal activities.

The information provided should address the following points in particular:

- The medicines prescribed over the long term must be taken regularly and must be monitored by means of compulsory medical follow-up.
- Instructions to be followed after a bone marrow transplant:
  - For several months after a bone marrow transplant, the patient must avoid very busy places, such as public transport, shopping centres, cinemas, parties, etc. Strict hygiene is essential to limit the risk of infection, and sex must be protected. In addition, the patient must remain in contact with the doctor and alert him or her at the slightest
sign that might suggest an infection (fever, pain, diarrhoea, etc.).

- A healthy lifestyle must include diet (avoiding food of doubtful origin or sandwiches prepared outside the home) and the need to avoid high-risk situations for the patient (sports, or violent blows that might cause bleeding). The patient must also wash his or her hands regularly, especially before eating, and avoid visiting anyone with influenza or any other known contagious infection. In addition, it is important to avoid self-medication and to obtain the doctor’s advice on any medicines taken.

- After the transplant, all vaccinations must be started again. By following these precautions, a transplant patient can, in principle, lead a normal life.

- These extreme early precautions can be gradually relaxed as the body readapts to its environment and recovers its normal functions.

- Lastly, since the medicines can have adverse effects on the foetus, a woman who wants to have a baby must discuss it first with the doctor.

3.4 Haematopoietic stem cell transplant

Allogeneic haematopoietic stem cell (HSC) transplant is the only potentially curative treatment today for MDS. It is generally reserved for high-risk MDS. It should be discussed on the basis of the patient’s age and whether there is a donor, related or not.

Nevertheless, some uncertainties remain:
- What kind of conditioning should be used for the transplant?
- Should the transplant be preceded by treatment, and intensive chemotherapy in particular?
- How quickly should the transplant be performed?

3.5 Pharmaceutical treatments

For simplicity, guides for doctors produced by HAS generally refer to categories of drugs without listing all the drugs indicated in the disease in question. However, each drug concerned is only to be considered within the actual framework of its Marketing Authorisation (MA). If for a specific reason this is not the case, and more generally, whenever a drug is prescribed in circumstances other than those given in the marketing authorisation, this is the sole responsibility of the prescriber, who must specifically inform the patient of this
In 2007, no medicinal product had a Marketing Authorisation for use in MDS.
Except in transplant cases, there is a consensus for separating ‘high-risk’ patients, who are those with a high or intermediate-2 IPSS score, from ‘low-risk’ patients, who include those with a low or intermediate-1 IPSS score.
Symptomatic treatment – principally red blood cell transfusions and the rapid treatment of infections in cases of neutropenia (Appendix 3) with broad-spectrum antibiotics – is fundamental in most types of MDS.

► Treatment of ‘high-risk’ MDS (high or intermediate-2 IPSS score) other than a transplant

The development of the hypomethylating agents azacitidine and decitabine (both substances licensed for temporary use by named patients) is changing the treatment of high-risk MDS by significantly increasing survival times.
- This treatment is now becoming the standard treatment for elderly patients.
- In younger patients, the value of hypomethylating agents compared with that of intensive chemotherapy is currently being assessed.

► Treatments for low-grade MDS
The purpose of these treatments is above all to correct cytopenias, principally anaemia:
- No treatment at all when the cytopenias are moderate or asymptomatic.
- When anaemia is symptomatic, try a treatment likely to prevent transfusions and to keep the haemoglobin (Hb) level permanently above 10–11 g/dl, rather than simple transfusion therapy in which the Hb level is by definition below 10 g/dl for much of the time, which is generally associated with clinical effects (fatigue, lower quality of life, etc.).
- Pharmaceutical treatment of anaemia:
  - high-dose recombinant EPO: this treatment should be given alone or in combination with G-CSF in patients with Hb < 9–10 g/dl and poor clinical tolerance for this anaemia, even if they are not transfused, in the absence of chromosome 5 deletion (del(5q)) in the karyotype (lenalidomide may be used off label for patients with this deletion). The response to treatment is observed for three...
months; if it is ineffective after this time, the treatment must be discontinued. **EPO and darbepoetin alfa did not have MAs for MDS in 2007.**

- **lenalidomide (off-label use):** in cases of transfusion-dependent anaemia in MDS patients with del(5q) and just a low-risk or intermediate-1-risk IPSS score; lenalidomide use has not been validated for patients with higher scores. In January 2008, the European Medicines Agency refused to grant a MA for lenalidomide in this indication because of doubt regarding an increased risk of acute leukaemia in MDS patients with del(5q) who are treated with lenalidomide. This treatment must therefore be initiated and monitored by a specialist, with regular full blood counts.

  If del(5q) patients prove resistant to lenalidomide, treatment will then rest on red blood cell transfusions and EPO.

- **thalidomide:** treatment proposed at low doses (50–200 mg/day) for patients with anaemia (Hb < 10 g/dl), an EPO level greater than 500 IU/l, or resistance to recombinant EPO, with bone marrow blastosis < 5% **(used in France under license for temporary use by named patients).**

- **antilymphocyte serum (off-label use):** in patients below the age of 60 years with EPO-resistant anaemia and at least one other cytopenia.

- **Treatment of neutropenia:**
  The use of G-CSF is not generally recommended; G-CSF might be considered for short periods in cases of serious infectious episodes in patients with major neutropenia without excess blasts.

- **Treatment of thrombocytopenia:**
  androgen therapy **(off-label use)**
  two thrombopoietin receptor agonists (AMG 531 and eltrombopag) are currently the subject of clinical research.

### Symptomatic treatments

- **Phenotyped packed red blood cell transfusions:**
  There is nothing special to remark on these, in comparison with other blood diseases, except for the fact that they should be considered in the long term and they are generally used in elderly patients whose tolerance of anaemia is mediocre.
A transfusion is recommended once Hb < 8, or at a higher level depending on the patient’s clinical tolerance and comorbidities (particularly frequent with generally elderly patients).

- **Platelet transfusions:**
  Given the need to consider this treatment in the long term and the risk that it may rapidly become ineffective due to allo-immunisation, indications for it should be restricted except in the case of myelosuppression treatments, surgical procedures or patients with a haemorrhagic syndrome.

- **Treatment of infections:**
  This is identical to the treatment of infections occurring more generally in neutropenic patients. In MDS, neutropenia is, however, often accompanied by a functional deficit of neutrophilic leucocytes (NL), increasing the infection risk.

  **It is recommended that MDS patients with neutropenia have an advance supply of broad-spectrum antibiotics to start taking at the slightest sign of infection.**

  No combinations have been studied prospectively. By analogy, the same combination may be proposed as that used in patients with chemotherapy-related neutropenia (amoxicillin-clavulanic acid 3 g per day plus ciprofloxacin 1 g per day).

- **Iron chelating treatments:**
  In regularly transfused patients, it is suggested that serum ferritin be monitored approximately every 3 months and iron chelating treatment be commenced for serum ferritin of 1000–2000 ng/ml, depending on the transfusion frequency.

  This treatment is indicated for patients whose prognosis is relatively good, i.e. with a low or intermediate-1 IPSS score, or who may be given active treatment. Treatment should continue for as long as the iron overload persists, unless the prognosis becomes unfavourable.

  Iron chelating treatment may be given either parentally with deferoxamine, or orally with deferasirox (MA as second-line treatment when deferoxamine is contraindicated or unsuitable) or deferiprone (off-label use).

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### 4. Follow-up of myelodysplastic syndrome patients

#### 4.1 Objectives

- To assess treatment efficacy
- To assess treatment safety (detection of undesirable effects)
To adjust the treatment
To evaluate compliance with the treatment
To evaluate disease progression
To evaluate improvement in the patient’s knowledge about his or her disease
To continue education and counselling of the patient and his or her family and friends
To investigate the development of any comorbidity

4.2 Professionals involved in follow-up

See the professionals involved in treatment.

Other healthcare professionals may be involved if complications arise that are directly linked to the progression of the disease.

4.3 Frequency and content of consultations

Follow-up of MDS patients should be conducted by the haematologist in close collaboration with the general practitioner.

Stable patients not receiving treatment (transfusion-free, NL > 10^9/l, platelets > 50 x 10^9/l) may be monitored alternately by the haematologist and the primary care doctor every 2–3 months. Patients receiving treatment should be followed up more frequently. The frequency of follow-up will depend on the patient's clinical condition.

4.4 Laboratory monitoring of treatment

► Post-transfusion monitoring

- Full blood count to determine the frequency of transfusion and assess the risk of infection.
- Monitoring of undesirable events:
  - investigation of alloimmunisation: test for immune antibodies one month after transfusion
  - test for iron overload (serum ferritin).

► Other laboratory tests

- Full blood count with reticulocyte count
- Blood smear cytology
- Bone marrow examination with blast percentage, evaluation of dysmyelopoiesis and Perls staining to determine the percentage of ring sideroblasts; this need not be done systematically in low-
risk MDS unless there is progression, but should be done regularly every 6 months in high-risk MDS

- Bone marrow karyotype in progressive cases or to assess treatment efficacy.
Appendix 1. Persons involved in preparing this guide

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- Dr Georges Andreu, transfusion haematologist, National Blood Transfusion Institute, Paris
- Prof. Pierre Bordigoni, haematologist, CHU Nancy
- Prof. François Dreyfus, haematologist, hôpital Cochin, Paris
- Prof. Pierre Fenaux, haematologist, hôpital Avicenne, Bobigny
- Prof. Bertrand Godeau, internist, hôpital Henri-Mondor, Créteil
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- Dr Norbert Vey, haematologist, Institut Paoli-Calmettes, Marseille
- Dr Francis Gaspari, medical adviser, CNAMTS (National Health Insurance Fund for Salaried Workers)
- Ms Sarah Jenny, ‘Connaître et combattre les myélodysplasies’ (‘Understand and fight myelodysplasias’) patient group, Paris
- Ms Sandrine Gricar, ‘HPN France - Aplasie médullaire’ (‘PNH France – Bone marrow failure’) patient group, Paris
# Appendix 2. MDS classifications

**French-American-British (FAB) classification of myelodysplastic syndromes, after Réseau ONCOLOR, 2006**

<table>
<thead>
<tr>
<th></th>
<th>Blasts in peripheral blood (%)</th>
<th>Blasts in bone marrow (%)</th>
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</thead>
<tbody>
<tr>
<td>Refractory anaemia (RA)</td>
<td>&lt; 1</td>
<td>&lt; 5</td>
</tr>
<tr>
<td>Refractory anaemia with ring sideroblasts (RARS)</td>
<td>&lt; 1</td>
<td>&lt; 5 with over 15% ring sideroblasts</td>
</tr>
<tr>
<td>Refractory anaemia with excess blasts (RAEB)</td>
<td>&lt; 5</td>
<td>5 – 20</td>
</tr>
<tr>
<td>Refractory anaemia with excess blasts in transformation (RAEB-T)</td>
<td>&lt; 5</td>
<td>21 – 30</td>
</tr>
<tr>
<td>Chronic myelomonocytic leukaemia (CMML)</td>
<td>&lt; 5</td>
<td>5 – 20</td>
</tr>
</tbody>
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A new classification was proposed by WHO in 1999:

**WHO classification of myelodysplastic syndromes, after Réseau ONCOLOR, 2006**

<table>
<thead>
<tr>
<th></th>
<th>Blood</th>
<th>Bone marrow</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refractory anaemia (RA)</td>
<td>Anaemia, blasts absent or rare</td>
<td>Erythroblast dysplasia only; &lt; 5% blasts</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt; 15% ring sideroblasts</td>
</tr>
<tr>
<td>Refractory cytopenia with multilineage dysplasia (RCMD)</td>
<td>Cytopenias; blasts absent or rare; no Auer rods; monocytes &lt; 1 x 10⁹/l</td>
<td>Dysplasia in at least 10% of cells and at least 2 myeloid lineages; &lt; 5% blasts; no Auer rods; &lt; 15% ring sideroblasts</td>
</tr>
<tr>
<td>Refractory anaemia with ring sideroblasts (RARS)</td>
<td>Anaemia, blasts absent</td>
<td>Erythroblast dysplasia only; &lt; 5% blasts; at least 15% ring sideroblasts</td>
</tr>
<tr>
<td>Refractory cytopenia with multilineage dysplasia and ring sideroblasts (RCMD-RS)</td>
<td>Cytopenias (2 or more lineages); blasts absent or rare; no Auer rods; monocytes &lt; 1 x 10⁹/l</td>
<td>Dysplasia in at least 10% of cells and at least 2 myeloid lineages; &lt; 5% blasts; no Auer rods; at least 15% ring sideroblasts</td>
</tr>
<tr>
<td></td>
<td>Blood</td>
<td>Bone marrow</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>--------------------------------------------</td>
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</tr>
<tr>
<td>Refractory anaemia with excess blasts 1 (RAEB-1)</td>
<td>Cytopenias; &lt; 5% blasts; no Auer rods; monocytes &lt; 1 x 10⁹/l</td>
<td>Uni- or multilineage dysplasia; 5–9% blasts; no Auer rods</td>
</tr>
<tr>
<td>Refractory anaemia with excess blasts 2 (RAEB-2)</td>
<td>Cytopenias; &lt; 5% to 19% blasts; Auer rods present or absent; monocytes &lt; 1 x 10⁹/l</td>
<td>Uni- or multilineage dysplasia; 10–19% blasts; Auer rods present or absent</td>
</tr>
<tr>
<td>Unclassifiable MDS</td>
<td>Cytopenias; blasts absent or rare; no Auer rods</td>
<td>Unilineage dysplasia (granulocyte or megakaryocyte lineage); &lt; 5% blasts; no Auer rods</td>
</tr>
<tr>
<td>MDS with 5q- deletion only</td>
<td>Anaemia: &lt; 5% blasts; normal or elevated platelets</td>
<td>Normal or elevated megakaryocytes with hypolobulated nuclei; &lt; 5% blasts, no Auer rods; 5q- deletion only</td>
</tr>
</tbody>
</table>

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The number and degree of cytopenias also has prognostic value. The prognosis is made worse particularly by the presence of neutropenia or thrombocytopenia; anaemia is very often present in the forms without excess bone marrow blasts.

Most cytogenetic abnormalities suggest a poor prognosis, especially when multiple. The cytogenetic abnormalities with the least severe prognostic value are an isolated 5q deletion, and perhaps an isolated 20q deletion and the isolated loss of the Y chromosome. The prognosis for these three abnormalities is substantially similar to that of a normal karyotype. The prognosis for chromosome 7 abnormalities (monosomy 7 or del(7q)), abnormalities involving 17p deletion and 3q abnormalities is particularly poor.
## Total score

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Score</th>
<th>Median Survival</th>
<th>Incidence of AML</th>
</tr>
</thead>
<tbody>
<tr>
<td>'Low’ risk group</td>
<td>0</td>
<td>5.7 years</td>
<td>25% in 10 years</td>
</tr>
<tr>
<td>‘Lower-intermediate’ risk group</td>
<td>0.5–1</td>
<td>3.5 years</td>
<td>25% in 3.3 years</td>
</tr>
<tr>
<td>‘Upper-intermediate’ risk group</td>
<td>1.5–2</td>
<td>1 year</td>
<td>25% in 1 year</td>
</tr>
<tr>
<td>‘High’ risk group</td>
<td>&gt; 2</td>
<td>4.5 months</td>
<td>75%</td>
</tr>
</tbody>
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Appendix 3. Emergency procedures

1. Abnormalities requiring emergency hospitalisation
   - Poorly tolerated fever and shock
   - Necrotizing ulcerative gingivitis or antibiotic-resistant mouth or throat infections
   - High fever after taking medicine
   - Antibiotic-resistant fever
   - Any fever associated with neutropenia of less than 500/mm$^3$
   - Palpable purpura with haemorrhagic syndrome
   - Thrombocytopenia of less than 10 000/mm$^3$, even without a haemorrhagic syndrome
   - Poorly tolerated anaemia (cardiovascular and cerebral)

2. Assessing anaemia tolerance

   In all cases of anaemia, signs of severity must be investigated before any therapeutic decision is made, particularly regarding transfusions: in addition to laboratory signs (Hb levels), there are certain functional signs (dyspnoea on the slightest effort, vertigo, poorly tolerated tachycardia, oedema, angina pectoris, signs of vascular deficiency, etc.); they depend on the intensity of the anaemia as well as the patient’s age, the rapidity of the onset of the anaemia, and the prior existence of other conditions, particularly cardiovascular diseases.

3. Management of a febrile patient with neutropenia

   In the community

   This is a diagnostic and therapeutic emergency requiring immediate attention in a specialist facility.

   In hospital

   Rule out expected agranulocytosis occurring in a patient who has had chemotherapy (phone the department that administered the chemotherapy).

   A repeat clinical examination should look for foci of infection and signs of poor haemodynamic tolerance. As the cell count is often very low (no NL), there is a risk that it will be falsely reassuring.
Management has three prongs: diagnosis, infection and monitoring

- Diagnosis:
  - investigate aetiology: medicines taken
  - bone marrow examination
  - stop any non-essential medication.

- Infection:
  - in an emergency: antibiotic treatment started no more than 6 hours after the onset of the fever, as soon as the samples have been taken and without waiting for the results, with a broad-spectrum antibacterial agent chosen on the basis of probability and secondarily adjusted, administered intravenously in suitable doses
  - preceded by: frequent blood cultures, urine cultures, or cultures of any microbiological sample of interest
  - insertion of a venous line
  - chest x-ray
  - measurement of SaO₂, which may have dropped early
  - patient isolation measures.

- Clinical and biological monitoring:
  - inform the pharmacovigilance centre in the event of drug-induced agranulocytosis
  - give the patient the list of contraindicated medicines.

4. Assess the haemorrhage risk in cases of thrombocytopenia

There is generally no spontaneous haemorrhage risk so long as platelets are > 30 x 10⁹/l, except in cases of associated thrombocytopathy (due to kidney failure or medication), active combined coagulation treatment, or a conducive lesion or process (e.g. gastrointestinal lesion or poorly controlled hypertension).

The spontaneous haemorrhage risk of a peripheral thrombocytopenia is increased where:
- the patient is given anticoagulants or antiplatelet agents or NSAIDs
- purpura is extensive or mucosal (oral blisters) or accompanied by visceral bleeding
- there are haemorrhages in the eye fundus
- platelets are < 20 x 10⁹/l
- the thrombocytopenia has a central origin
- There is associated DIC (even biological)
● there is an anatomical factor for bleeding: a potentially haemorrhagic mucosal or vascular lesion.

Any invasive procedure (invasive surgery, surgery exposing the patient to a traumatic procedure, or an intramuscular injection) must first be discussed with the specialist.
Appendix 4. References


